# Health technology assessment of imaging technologies for breast cancer screening and follow-up

Koleva-Kolarova, Rositsa Georgieva

# Chapter 1.
# General introduction

### *Incidence and epidemiology of primary and metastatic breast cancer*

Breast cancer is the second most commonly diagnosed cancer and ranks as the fifth cause of death worldwide[1] with 5-10% of the primary cases diagnosed at an advanced stage[2]. The incidence and prevalence of primary breast cancer increased with the introduction of regular mammographic screening and adjuvant systemic and targeted therapies.[3] Despite the relatively high 5-year age-adjusted survival rate (80%)[4], local recurrences and distant metastases are still common. Reportedly, locally recurrent breast cancer occurs in 5-10% of all patients with primary operable breast cancer[5], while distant relapses affect approximately 10% of the patients within 5 years after primary disease and treatment.[6,7] The incidence of locally recurrent disease is highest amongst younger women with high tumour grade and size.[5] The incidence of metastatic breast cancer is highest in the first 2 years, slowly decreases till the fifth year and remains relatively constant thereafter.[7,8] More than three-quarters of the locally recurrent breast cancers are diagnosed in the ipsilateral breast or chest wall with clinically negative axillary nodes.[9] The most common sites for metastatic breast cancer are bone, lung/pleura, liver, lymph nodes and brain.[7,8,10] While local recurrences might be treated with a curative intent when possible (e.g. localised tumour and lack of distant spread), once breast cancer has metastasised to distant locations, it is generally considered amenable to palliative rather than curative care, and the goals of treatment at this later stage are focused on delaying the progression of the metastatic disease, relief of cancer-related symptoms and maintaining quality of life.[2]

### *Recommendations for breast cancer screening, follow-up and treatment*

The European society for medical oncology (ESMO) recommends regular mammographic screening in women aged 50–69 years. As there is no consensus and evidence regarding regular

screening in women aged 40–49 years, ESMO does not recommend regular screening in that age group.[3]

Regular breast cancer screening has been implemented in eighteen European countries to detect breast cancer at an early stage and decrease mortality from the disease. In these programmes the onset of regular screening is usually at the age of 50, however, some countries (United Kingdom, Czech Republic) and regions (e.g. in Sweden and Italy) invite women younger than 50 years to be screened despite the controversy in the benefit-harm balance.[11,12]

Mammographic screening has been shown to decrease the mortality from breast cancer, however, the exact effect is debatable and varies between 10% to 20% mortality reduction from breast cancer in the age group 50-69 years[13–16] with some research groups even arguing that there is no sound proof of regular screening leading to disease specific mortality reduction[13]. Reviews and meta-analyses of randomised controlled trials highlight the importance of considering not only mortality reduction, but also false-positives, false-negatives, overdiagnosis, and overtreatment when balancing the benefits and harms of screening.[3]

ESMO recommends that patients with primary breast cancer are subjected to regular follow-up visits including physical examination and symptoms elicitation to detect early local recurrences or contralateral breast cancer. Routine screening for metastatic recurrence in asymptomatic breast cancer patients is usually not recommended as there is no evidence that it can impact survival.[3]

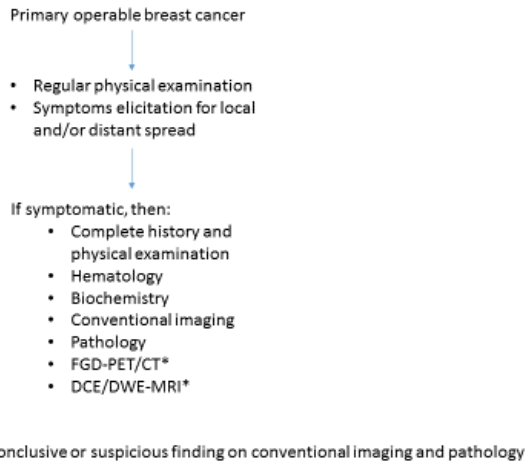
In case of clinical suspicion (Figure 1) or symptoms suggestive for distant spread, ESMO recommends a minimal staging work-up which should include a complete history and physical examination, hematology and biochemistry tests, imaging of chest, abdomen and bone.[2] The standard imaging work-up for diagnosing metastatic breast cancer includes conventional imaging with bone X-ray and/or bone scintigraphy, chest X-ray and/or chest computed tomography (CT), liver ultrasound and/or abdominal CT, and magnetic resonance

imaging (MRI). Histological biopsies are advised to confirm findings and re-evaluate tumour receptor status (oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)) of the metastatic disease.[2,17] When findings on conventional imaging are equivocal or when histology from the suspicious lesion cannot be obtained, positron emission tomography (PET) and CT (PET/CT) with 2-[18F]fluoro-2-deoxy-D-glucose (FDG), dynamic contrast-enhanced (DCE) or diffusion-weighted imaging (DWI) MRI are acceptable options to further evaluate suspected metastatic disease.[2,17]

One of the most important prognostic factors in both early breast cancer and metastatic disease is expression of ER, PR and HER2 in tumour cells. This expression also allows selecting patients for endocrine- and anti-HER2 treatments. Endocrine therapy is recommended in all patients with detectable ER expression (defined as ≥1% of invasive cancer cells) irrespective of whether they are eligible for chemotherapy and/or anti-HER2 targeted therapy.[18,19] Anti-HER2 therapy with or without chemotherapy is prescribed to patients with HER2-positive disease. There is no evidence to support the choice of therapy in case of discordance in hormone receptor (ER and PR) or HER2 status between primary and metastatic tumour. Therefore, it is recommended that in case receptors are positive, targeted therapy (endocrine and/or anti-HER-2 therapy) should be provided.[2,3]

Novel diagnostic and treatment options are continuously being investigated in randomised clinical trials urging the need to integrate their findings into everyday clinical practice. In order to decrease the uncertainty from variation in clinical medicine and to ensure the adoption of these developments which have proven to be efficient, decision-analytic modelling and health technology assessment can be employed.

**Figure 1.** Minimal diagnostic work-up for suspected local or distant recurrence after primary breast cancer[2]




### *Health technology assessment and use of decision analytical models to inform decision making in breast cancer screening, follow-up and treatment*

Health technology assessment (HTA) is defined as "the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods.[20]

The use of decision-analytic modelling for the purpose of performing HTA has increased in the last years.[21] A variety of decision analytical models, using mathematical, statistical, and computer simulation, is increasingly being utilised for economic evaluation of screening, follow-up and treatment interventions in breast cancer.[22] These models are important for decision making in health care because they are able to synthesise data from multiple

sources and estimate the effects of interventions in situations when clinical trials are not feasible because of time, costs, ethical or other considerations.[23]

Breast cancer is a particular field where randomised controlled trials require a long follow-up time and large groups of participants in order to assess the effects on mortality reduction, and the potential benefits and harms associated with different programmes and interventions[13–16] for screening, follow-up and treatment. Therefore, simulation models are often applied along with clinical trials to ensure proper evaluation of the effects of these health interventions. Simulation models provide the opportunity to evaluate different health services, compare scenarios and extrapolate the results to different population sub-groups in order to find the optimum policy without having to trial each variant. As simulation models are being more widely used to inform decision making, the reliability and the accuracy of their outcomes are essential. Guidelines have been introduced to provide frameworks and directions for developing decision analytical models.[21–24]

### *Thesis aim and outline*

Breast cancer is a leading cause of morbidity and mortality worldwide. Applying imaging modalities is aimed at detecting primary and advanced disease at an early stage in order to increase survival in these patients. However, before the imaging techniques can be widely implemented into clinical practice their expected benefits, harms and cost-effectiveness should be assessed. Therefore, performing (early) health technology assessment is essential to inform decision making and guide implementation of screening and diagnostic imaging technologies. The aim of the research project presented in this thesis is to perform health technology assessment of imaging modalities applied for screening for primary breast cancer, and follow-up and treatment selection in metastatic disease.

**Chapter 2** presents a critical evaluation of published simulation models for breast cancer screening of the general population and provides a direction for future modelling. We developed and applied a framework for qualitative assessment of published simulation models for breast cancer screening of the general population. The framework incorporated model type; input parameters; modelling approach, transparency of input data sources/assumptions, sensitivity analyses and risk of bias; validation, and outcomes. In order to assess the accuracy of models' outcomes we compared predicted mortality reduction and cost-effectiveness to estimates from meta-analyses of randomised controlled trials for breast cancer screening and acceptability thresholds.

Breast cancer screening has been implemented in many European countries to detect breast cancer at an early stage and decrease breast cancer mortality. The age of 50 years is usually considered to be the optimal to start screening, however, there are arguments which suggest that women from the general population may benefit from regular breast cancer screening starting at an earlier age. Therefore, in **Chapter 3** we performed a comprehensive evaluation regarding the proper balance of harms and benefits, and the cost-effectiveness of regular breast cancer screening starting at a younger age. The setting for this analysis was the Dutch general breast cancer screening programme where biennial screening among women aged 50-74 is already available. We assessed the impact of lowering the starting age of breast cancer screening from 50 to 48 and 46 years of age to the number of tumour deaths prevented, years of life saved, number of false positives, radiation-induced tumours, costs and cost-effectiveness. Molecular imaging with positron emission tomography (PET) and computed tomography (PET/CT) using different tracers was found to improve the diagnosis and treatment decision making in patients with a history of ER-positive breast cancer presenting with a clinical dilemma on conventional imaging. As guidelines only recommend the addition of FDG-PET/CT to diagnostic work-up when conventional imaging is inconclusive, there is no

clarity on the impact of FES-PET/CT on diagnosis of metastatic breast cancer. Therefore, in **Chapter 4** we examined the effect of upfront PET/CT with the tracers FES and FDG on the number of performed biopsies and associated costs when applied to diagnosing metastatic breast cancer. The aim of this study was to evaluate the effect on the number of performed biopsies and costs associated with implementing FES or FDG-PET with contrast-enhanced CT as an upfront imaging test for diagnosing ER-positive metastatic breast cancer in comparison with the standard work-up in women presenting with symptoms.

Metastatic breast cancer patients are subjected to palliative rather than curative intent and the type of treatment they are assigned to depends on the receptor status of their tumours. Significant advances in molecular targeted therapies and the development of new treatment combinations can offer personalised and less aggressive approach of managing patients with distant relapse that have overexpressing receptor status. Targeted therapies could prolong life of metastatic breast cancer patients, however, the extent to which they could increase their survival is not yet clear. Therefore, in **Chapter 5** we performed a systematic review and meta-analysis of published randomised controlled trials in order to assess the clinical effectiveness of targeted therapies in terms of increase in months in median progression-free and overall survival of patients diagnosed with advanced or metastatic breast cancer.

Treatment options for metastatic breast cancer can potentially prolong the survival of these patients, but can be costly and may be associated with adverse effects. In addition, not all patients benefit from first-line therapy, therefore, a personalised approach for treatment selection can be crucial to optimise patient outcomes at acceptable costs, and minimise adverse effects for those who would not have responded anyway. Currently treatment selection for patients with metastatic breast cancer is based on the receptor status of the tumours as reported by pathology results. However, pathology can be inconclusive and does not provide whole body tumour characterisation. Molecular positron emission tomography (PET) imaging with

different tracers can give insight into the characteristics of the tumour lesions, but it is currently not recommended as a standard diagnostic modality and there is no clarity of the economic impact of PET/CT for treatment selection in metastatic breast cancer. Therefore, in **Chapter 6** we performed an economic evaluation and assessed the potential cost-effectiveness of applying PET to select first-line treatment in metastatic breast cancer patients with non-rapidly progressive disease.

**Chapter 7** presents a general discussion of the most important findings of this thesis and conclusion.

**References:**


1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359–86.
2. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E, ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23: vii11–9.
3. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 Suppl 5: v8–30.
4. IKNL (2016) Available at http://www.cijfersoverkanker.nl (accessed 15 June 2016).
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707–16.
6. Hurk van den CJG, Eckel R, Poll van de-Franse LV, et al. Unfavourable pattern of metastases in M0 breast cancer patients during 1978-2008: a population-based analysis of the Munich Cancer Registry. Breast Cancer Res Treat 2011; 128: 795–805.
7. Lord SJ, Marinovich ML, Patterson JA, et al. Incidence of metastatic breast cancer in an Australian population-based cohort of women with non-metastatic breast cancer at diagnosis. Med J Aust 2012; 196: 688–92.
8. Miller KD. Breast cancer: in Handbook of Advanced Cancer Care. In Fisch MJ, Bruera E (eds), 2003; vol. 500, pp 150–161. Cambridge University Press: Cambridge, UK.
9. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–933.
10. Sihto H, Lundin J, Lundin M, et al. Breast cancer biological subtypes and protein expression predict for the preferential distant metastasis sites: a nationwide cohort study. Breast Cancer Res 2011; 13: R87.
11. Paci E and the EUROSCREEN Working Group. Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. J Med Screen 2012; 19 Suppl1: 5–13.
12. Forouzanfar MH, Foreman KJ, Delossantos AM, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet 2011; 378: 1461–84.
13. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2013. http://dx.doi.org/10.1002/. 14651858.CD001877.pub5. Issue 6. Art. No.: CD001877. p.10.
14. Independent UK panel on breast cancer screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012; 380: 1778–86.
15. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. preventive services task force. Ann Intern Med 2009; 15: 727–37.
16. The Canadian Task Force on Preventive Health Care. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. CMAJ 2011; 183: 1991–2001.
17. NCCN Guidelines Version 2.2016. Available at http://www.NCCN.com (accessed 15 June 2016).
18. International Breast Cancer Study Group, Colleoni M, Gelber S, et al. Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group trial 13–93. J Clin Oncol 2006; 24: 1332–41.
19. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–1717.
20. HTA glossary. International Network of Agencies for Health Technology Assessment and Health Technology Assessment international (http://www.htaglossary.net/, accessed on 15 June 2016).
21. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modeling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics 2006; 24(4):355–71.
22. Stout NK, Knudsen AB, Kong CY, McMahon PM, Gazelle GS. Calibration methods used in cancer simulation models and suggested reporting guidelines. Pharmacoeconomics 2009; 27: 533–45.
23. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics 2006; 24: 1043–53.
24. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices – overview: a report of the ISPOR-SMDM modeling good research practices task force-1. Value Heal 2012; 15:796–803.